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10/597,865	08/10/2006	Ian Timothy William Matthews	065435-9033-US01	7279

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EXAMINER	
CLARK, SARA E	
ART UNIT	PAPER NUMBER
1612	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/597,865	MATTHEWS ET AL.	
	Examiner	Art Unit	
	SARA E. CLARK	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/10/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

NON-FINAL REJECTION

This application is a 35 U.S.C. 371 (national stage) application of PCT/GB05/00496, filed 2/11/2005, claims benefit of priority to provisional application 60/544,778, filed 2/13/2004. Claims 1-11, as amended, are pending.

Priority

1. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. The instant claims are supported by the disclosure of provisional application 60/544, 778; therefore, claims 1-11 are entitled to an effective filing date of 2/13/2004.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on 8/10/2006 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Claim Objections

3. Claims 1, 5, 6, 7, 10, and 11 are objected to because of the following informalities: the compounds recited are identified only by abbreviations (e.g., "AQ4," "AQ4N," some of which are not explained or elaborated upon in the specification, further obscuring Applicant's intent. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Scope of Enablement

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for salts of the claimed compounds, does not reasonably provide enablement for their solvates. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. As recognized by MPEP 2164.01(a), "there are several factors to consider when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." *In re Wands*, 8 USPQ2d 1400 (1988), sets out these factors, which include:

A. The Nature of the Invention. The nature of the invention is an improvement on known processes for preparing a known compound from known reactants and known intermediates that does not extend to the preparation of any particular solvate, only salts and solvates of the final product.

B. The Breadth of the Claims. The breadth of claims 1-6 goes beyond the disclosure; specifically, the instant claims encompass any solvate of the claimed compounds.

C. The State of the Prior Art and the Level of Predictability in the Art. Active pharmaceutical ingredients are frequently delivered to the patient in the solid-state as part of an approved dosage form (e.g., tablets, capsules, etc.). Solids provide a convenient, compact, and generally stable format to store an active pharmaceutical ingredient or a drug product. Understanding and controlling the solid-state chemistry of active pharmaceutical ingredients, both as pure drug substances and in formulated products, is therefore an important aspect of the drug development process. Active pharmaceutical ingredients can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co-crystals, and amorphous solids. Each form displays unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability, and other performance characteristics of the drug. Hence, it is critical to understand the relationship between the particular solid form of a compound and its functional properties.

For ionizable compounds, preparation of salt forms using pharmaceutically acceptable acids and bases is a common strategy to improve bioavailability. However, the preparation of other solid forms such as solvates are not so common as to be predictable. In order to obtain patent protection on these forms, some of which may have significantly different properties and relevance as development candidates, it is essential to prepare them, identify conditions for making them, and evaluate their properties as valuable new pharmaceutical materials. A large number of factors can influence crystal nucleation and growth during this process, including the composition of

the crystallization medium and the processes used to generate super-saturation and promote crystallization (Morissette et al., 2004, 56, 275-300).

Crystalline solids can exist in the form of polymorph, solvates or hydrates. "Phase transitions such as polymorph interconversion, desolvation of solvate, formation of hydrate, and conversion of crystalline to amorphous form may occur during various pharmaceutical processes, which may alter the dissolution rate and transport characteristics of the drug. Hence, it is desirable to choose the most suitable and stable form of the drug in the initial stages of drug development" (Vippagunta et al., 2001, 3-26, abstract). In further discussing the predictability of the formation of solvates, Vippagunta et al. disclose that "predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds" (page 18, section 3.4). Therefore, for these reasons, the state of the art must be regarded as highly unpredictable.

D. The Amount of Direction or Guidance Present and Presence or Absence of Working Examples. The only direction or guidance present in the specification is for the synthesis of 1,4-bis{[2-(dimethylamino-N-oxide)ethyl]amino}-5,8-dihydroxy-anthracene-9,10-dione (AQ4N), as well as salts and solvates thereof. While the disclosure provides guidance as to the preparation of salts of AQ4N, “solvate” is defined only briefly and generically (specification, p. 14, lines 4-8), and provides no direction or instruction for the preparation of solvates of AQ4N.

E. The Amount of Direction or Guidance Present and Presence or Absence of Working Examples. No working examples are provided in the disclosure for the preparation of solvates of AQ4N.

F. The Quantity of Experimentation Needed and the Level of Skill in the Art. While the level of skill in the pharmaceutical arts is high, it would require undue experimentation for one of ordinary skill in the pertinent art to prepare any solvate AQ4N. The science of crystallization has evolved such that, without guidance or working examples in the specification, the claims lack enablement.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 7 and 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (J. Chem. Soc., Perkin Trans. 1, 2755-58, 1999, provided by Applicants on the IDS dated 8/10/2006).

Lee et al. teach a method for the synthesis of 1,4-bis{[2-(dimethylamino-N-oxide)ethyl]amino}-5,8-dihydroxy-anthracene-9,10-dione (AQ4N) by the oxidation of AQ4 (1,4-bis{[2-(dimethylamino)ethyl]amino}-5,8-dihydroxy-anthracene-9,10-dione). Preparatory to this oxidation step, Lee et al. also disclose how to make the precursor

compound DDA (1,4-difluoro-5,8-dihydroxy-anthracene-9,10-dione), by the reaction of p-hydroquinone with difluoro-phthalic anhydride (DFPA), as recited in claim 7 (scheme 2, p. 2755; col. 2, p. 2757. Lee et al. teach this reaction step using powdered anhydrous aluminum chloride, well-mixing the reactants by shaking, heating the reaction mixture to 200ºC, ±5ºC, over a period of one to two hours, so that the melted reaction mixture serves as its own solvent. With the exception of the limitation of the reaction temperature not to exceed 200ºC as recited in claim 7, the present disclosure employs the same reactants and reagents, which are stirred in a solvent rather than shaken (specification p. 14, lines 16-25). Thus, Lee et al. differs from claim 7 only in the reaction temperature, and explicitly discloses temperatures under 200ºC (i.e., 195ºC). As recognized by MPEP §2144.05,

> Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

After the completion of the Friedel-Crafts acylation step using aluminum chloride, Lee et al. disclose the addition of concentrated hydrochloric acid to the reaction mixture and stirring overnight to give the crude DDA (1,4-difluoro-5,8-dihydroxy-anthracene-9,10-dione), which was used in the next synthetic step without further purification (p. 2757, col. 2), corresponding to the step of slurrying crude DDA with aqueous hydrochloric acid as recited in claim 9. Further, according to the method of Lee et al., the next step, synthesis of AQ4 from DDA, begins with adding to DDA a five-fold molar excess of *N*,*N*-dimethyl-ethylenediamine in pyridine solvent (p. 2757, col. 2), both of

which have a nitrogen atom with a lone pair of electrons and thus can act as chelating agents, as recited in claim 10.

Lee et al. also teach the synthesis of AQ4 (1,4-bis{[2-(dimethylamino)-ethyl]amino}-5,8-dihydroxy-anthracene-9,10-dione), by reacting DDA (1,4-difluoro-5,8-dihydroxy-anthracene-9,10-dione) with N,N-dimethyl-ethylenediamine in pyridine at room temperature, then pouring the mixture into brine, stirring at 0ºC for two hours, and washing with ammonium hydroxide (p. 2757, col. 2), as recited by claim 11. As noted in the International Preliminary Report on Patentability (dated 8/14/2006, para. 4.3), claim 11 differs from the prior art only in that the reaction is treated with a combined solution of ammonium hydroxide and brine, rather than being treated with brine in one step and ammonium hydroxide in a second step, such that an inventive step (nonobviousness) could be acknowledged only if this led to unexpected results. See MPEP §2144.04 (citing *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) (selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results); *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (Selection of any order of mixing ingredients is *prima facie* obvious).

8. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (J. Chem. Soc., Perkin Trans. 1, 2755-58, 1999, provided by Applicants on the IDS dated 8/10/2006), as applied to claims 7 and 9-11 above, and further in view of Olah et al. (Kirk-Othmer Encyclopedia of Chemical Technology, Friedel-Crafts reactions, pp. 159-199, 2001).

As described above, Lee et al. teach a method for synthesizing the AQ4N precursor compound DDA (1,4-difluoro-5,8-dihydroxy-anthracene-9,10-dione) by the reaction of p-hydroquinone with difluoro-phthalic anhydride (DFPA), using powdered anhydrous aluminum chloride. As described in the specification (p. 8, lines 20-27), this step is a Friedel-Crafts acylation, which takes advantage of the catalytic effect of aluminum chloride. However, Lee et al. do not disclose the use of tetramethylene sulfone (sulfolane) as a solvent for this reaction, as recited in claim 8.

As taught by Olah et al., tetramethylene sulfone is known in the art as a suitable solvent for Friedel-Crafts acylations (p. 182, last paragraph), which include the nitration of anthracenes and in the synthesis of benzophenones, dihydroxytetrahydro-napthacenediones, and anthracyclinones (pp. 174-175). As recognized by MPEP §2144.07, it is *prima facie* obvious to substitute art-recognized equivalents known for the same purpose (see, e.g., *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982); and *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)).

9. Claims 1 and 3-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (J. Chem. Soc., Perkin Trans. 1, 2755-58, 1999, provided by Applicants on the IDS dated 8/10/2006), in view of Smith et al. (WO99/65992, published 12/23/1999) and Patterson (US Pat. 5,132,327, issued 7/21/1992) in combination.

Lee et al. teach a method for the preparation of 1,4-bis{[2-(dimethylamino-N-oxide)ethyl]amino}-5,8-dihydroxy-anthracene-9,10-dione (AQ4N) by the oxidation of AQ4 (1,4-bis{[2-(dimethylamino)ethyl]amino}-5,8-dihydroxy-anthracene-9,10-dione)

using the peracid MCPBA (*m*-chloro-peroxybenzoic acid as the oxidizing agent, as recited in claim 1, and using dichloromethane as the solvent (scheme 1, col. 1, p. 2755), as recited in claim 4. Lee et al. also disclose the use of 3-phenyl-2-(phenylsulfonyl)-oxaziridine in dichloromethane as the oxidizing agent, and stirring the mixture at 0°C only after this addition (p. 2758, col. 1).

In addition, Lee et al. teach the preparation of the dihydrochloride salt of AQ4N by reacting AQ4N with a solution of hydrogen chloride, which is achieved by bubbling anhydrous HCl gas through the solution at 0°C until the pH is about 1 (p. 2758, col. 1), as recited by claim 5. Finally, purification of DRAQ5N and AQ4 by silica gel column chromatography is disclosed by Smith et al. (p. 13, line 26) and Lee et al. (p. 2757, col. 2), respectively. Silica gel is known in the art as a common adsorbent used in the removal of contaminants and impurities, as is activated charcoal, recited in claim 6, which would be an obvious variant (see Sigma-Aldrich adsorbents).

As recognized by MPEP §2144.07, it is *prima facie* obvious to substitute art-recognized equivalents known for the same purpose (see, e.g., *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982); and *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)). “Reading a list and selecting a known compound to meet known requirements is no more ingenious than selecting the last piece to put in the last opening in a jig-saw puzzle.” 325 U.S. at 335, 65 USPQ at 301).

However, Lee et al. do not explicitly teach a reaction temperature not exceeding 10°C or addition of the oxidizing agent at a temperature not exceeding 0°C, as recited in

claim 1, or conducting the reaction at a temperature not exceeding 0°C, as recited in claim 3.

Patterson teaches the addition of *m*-chloro-peroxybenzoic acid as the oxidizing agent to a solution of AQN dissolved in dichloromethane, already cooled to 0°C in an ice bath (Example 5). Thus, the method of Patterson discloses addition of the oxidizing agent at a temperature not exceeding 0°C, as recited in claim 1. However, the oxidation reaction of Patterson is allowed to come to room temperature (20-25°C).

Smith et al. teach the synthesis of a close analog of AQ4N, the symmetrical DRAQ5N ([1,5-bis-((2-dimethylamino-N-oxide)ethyl)amino)-4,8-dihydroxy-anthracene-9,10-dione) from the analogous precursor DRAQ5 by oxidation with the peracid *m*-chloroperoxybenzoic acid in dry dichloromethane, where the reaction mixture is left overnight at -20°C (p. 13, lines 20-25). Thus, the method of Smith discloses a reaction temperature not exceeding 10°C, as recited in claim 1, and conducting the reaction at a temperature not exceeding 0°C, as recited in claim 3.

Advantages of using a lower temperature would be to slow the reaction speed and ensure its completeness, so as to maximize the use of expensive starting compounds as well as minimize side reactions and the formation of undesired by-products. This would have the follow-on advantage of reducing costly and labor-intensive purification procedures.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art to prepare AQ4N from AQN, as taught by Lee et al., using the reagents taught by both Lee et al. and Smith et al., at the temperature taught by Smith et al., because the

completeness of reactions and quality of the product is a particularly high priority in the synthesis of compounds destined for pharmaceutical use.

10. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (J. Chem. Soc., Perkin Trans. 1, 2755-58, 1999, provided by Applicants on the IDS dated 8/10/2006), in view of Smith et al. (WO99/65992, published 12/23/1999) and Patterson (US Pat. 5,132,327, issued 7/21/1992), as applied to claims 1 and 3-6 above, and further in view of Dongre et al. (Synth. Comm. 31(2): 167-172, 2001).

As discussed above, Lee and Smith teach a method of preparing dihydroxy-di-(2-dimethylamino-N-oxide)ethyl)amino-anthracene-9,10-diones using the peracid *m*-chloro-peroxybenzoic acid as the oxidizing agent in dichloromethane.

However, neither Lee nor Smith teach the use of the peracid salt magnesium monoperoxyphthalate as the oxidizing agent.

Dongre et al. teach the use of a variety of oxidants for the oxidation of tertiary nitrogen compounds to N-oxides, specifically identifying *m*-chloro-peroxybenzoic acid and magnesium monoperoxyphthalate as oxidizing agents for this transformation (p. 167), as recited in claim 2. As recognized by MPEP §2144.07, it is *prima facie* obvious to substitute art-recognized equivalents known for the same purpose (see, e.g., *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982); and *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)).

Conclusion

11. Claims 1-11 are rejected.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARA E. CLARK whose telephone number is (571) 270-7672. The examiner can normally be reached on Mon - Thu, 7:30 am - 5:00 pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass, can be reached at 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SARA E. CLARK/
Examiner, Art Unit 1612

/Frederick Krass/
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